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| 08/338,282 | 11/14/94 | WAYNER | E HUTCHINSONVL |

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| GAMBEL, P | |

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**DATE MAILED:** 04/17/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 11/14/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

**Part II SUMMARY OF ACTION**

1. ☐ Claims 1-5, 32, 34-36 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 6-31, 33, 37-63 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5, 32, 34-36 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

**EXAMINER'S ACTION**

15. Claims 6-31, 33 and 37-63 have been canceled. Claims 1-5, 32 and 34-36 are pending.

16. Applicant should update the status of parent USSN 07/814,873 on the first line of the specification.

17. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 16. Applicant will submit formal drawings upon the indication of allowable subject matter.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Applicant has not disclosed how to use $\alpha 4\beta 1$-specific antibodies therapeutically in humans. There is insufficient information or nexus with respect to the in vivo operability of $\alpha 4\beta 1$-specific antibodies to use applicant's invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

Concerning antibody therapy in general, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993).

Furthermore, it is well known in the art that the clinical efficacy of antibody therapy including humanized antibodies have been limited by specificity, binding constants, tissue penetration, clearance rates and the mode of action of the effector are presented. Therefore, the art indicates that even humanized antibodies are not necessarily predictable in their efficacy. For example, Mountain et al. teach that most antibody-based therapies are very unlikely to achieve success with a single dose (Biotechnology and Genetic Engineering Reviews, 10: page 11, paragraph 1, first sentence, 1993). The success of multiple dosing as a therapeutic regimen alleged by applicant is contrary to that experienced in the art. Murine antibodies are limited to one or perhaps two doses and the administration of further doses leads to accelerated clearance and in many cases to complete abrogation of efficacy (Mountain et al., pages 10-11, overlapping paragraph).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). In a brief review of adhesion therapy, Shaffer relays similar concerns about monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993).

In a very recent update, Ward et al. addresses the issues associated with selection of interventions of adhesion molecules as an approach to anti-inflammatory therapy (Therapeutic Immunol., 1994). At the current time of the article (1994), in humans, there are relativley few conditions in which there is clear-cut evidence of the presence and participation of given adhesion molecules in humans (page 166, column 1, paragraph 1). Also, monoclonal antibodies are not likely to be the ultimate approach for in vivo blocking of adhesion molecules, even though they will likely provide important information (see pages 167-170, particularly Concluding Remarks).

The examiner maintains that in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunotherapeutic drugs can be species- and model-dependent, it is not clear that reliance on in vitro inhibition of binding by human cell lines (instant application) or in vivo inhibition of an experimental animal model (Yednock et al., Nature, 1992; filed 9/19/94, Paper No. 26) accurately reflects the relative efficacy of the claimed therapeutic strategy.

Therefore, it is not clear from the specification whether α4β1-specific antibodies can inhibit lymphocyte adherence or migration in humans and to what degree. Therefore, it does not appear that the asserted operability of the claimed method and compositions for inhibiting lymphocyte adherence and migration in vivo in humans would be enabled in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention, ~~using the teaching of the specification alone~~.

It is noted that Ward et al. and Mountain et al. cited above have been provided as additional references to support the examiner's position concerning the art-known limitations of antibody-based anti-adhesion therapy.

The following paragraphs are a reiteration of the examiner's rebuttal in response to applicant's After Final amendment, filed 9/19/94.

The examiner agrees that it is apparent that immunotherapy can be effective when applied to a highly defined model of inflammatory disease such as autoimmunity. However it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process. Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing autoimmune response (which is the usual case) or whether it is effective only in terms of prevention. Generally, such diseases are diagnosed only after significant tissue damage has occurred.

With respect to applicant's reliance on the effects of α4β1-specific antibody in a murine EAE model for multiple sclerosis (Yednock et al., Nature, 1992), multiple sclerosis is one of the most difficult disease in which to judge the effect of therapy since its natural history is unpredictable (Ebers, Lancet, 1994, particularly the first paragraph). Ebers further support the examiner's position above by stating that experimentally suppressing the secondary immune response anticipated in human autoimmune disease is much more difficult than suppressing the primary response to which therapy is directed in a transplant setting (e.g. experimental setting, see page 275, column 2, paragraph 2).

Similarly, applicant's arguments that the claimed invention

in the suppression of the immune and autoimmune responses in a wide range of diseases appears contrary to art-known limitations of animal models. For example, Brennan reviews those studies performed in animal models of arthritis which have investigated the role of cytokines in contributing to the pathogenesis of arthritis (Clin. Exp. Immunol., 1994). Although the animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses much more slowly over many years, with natural periods of disease exacerbation and remission. Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Curr. Opin. Immunol., 1992; see entire document, particularly page 558, column 2). Again, applicant's assertions on the predictability of in vitro assays and animal models does not appear to be consistent with art-known experience. Human diseases comprise multiple immune responses that makes therapeutic intervention a major hurdle even for known diseases.

Clearly, Harris et al. state that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). It is noted that this conference is the major annual meeting in the field of therapeutic monoclonals (page 44, column 1). The examiner maintains his reading of this clear statement rather than applicant's assertion. Waldmann clearly states that despite the wide ranging interest in monoclonal antibody therapy, the magic bullet of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved to be elusive (page 1657, paragraph 3). Only one monoclonal antibody, OKT3, has been licensed for clinical use. Applicant's concerns over the examiner's comments on the FDA are misplaced, as it was provided in this context as set forth by Waldmann. Furthermore, Jolliffe discloses that while OKT3 is effective for renal allograft rejection, OKT3 therapy for autoimmune diseases such as diabetes, multiple sclerosis and systemic lupus erythematosus has not been possible (Intern. Rev. Immunol., 1993).

Therefore, applicant's assertions that one of skill in the

art would be able to treat immune diseases with predictability and without undue experimentation is not believable in view of art. Applicant has not provided sufficient evidence or nexus a priori that establishes the efficacy of the instant treatment of human disease with α4β1-specific antibodies that is commensurate with the claimed invention. ~~Therefore, it does not appear that the asserted utility and operability of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art~~.

Applicant's arguments were fully considered but were not found convincing.

The rejection is maintained for the reasons of record.

20. Claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification (see sections 18-19).

21. Claims 34-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-36 are indefinite in that lack proper antecedent basis, since they depend on a canceled claim.

The amendments must be supported by the specification so as not to add any new matter.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

24. Claim 1, 2, 32 and 34 are rejected under 35 U.S.C. § 102(e) as being anticipated by Butcher (U.S. Patent No. 5,403,919). Butcher teaches the in vivo inhibition leukocyte-entodthelial interactions and leukocyte extravasation by the MEL-14 monoclonal antibody (see column 2, particularly, lines 2-7 and 35-65). The MEL-14 antibody binds the α4 component of the claimed α4β1 specificity.

25. Claims 1-5, 32 and 34-36 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher (U.S. Patent No. 5,403,919) in view of Hemler et al. (EP 0 330506) and Takada et al. (Nature, 1987). Claims 1-5, 32, 34-36 are drawn to treating to methods of inhibiting leukocyte-endothelial adherence and leukocyte migration with α4β1-specific antibodies.

It is noted that the claimed α4β1 specificity reflects two components, that is, an α4 component and a β1 component. Further, each component has been known to associate with different members of either the α or β family. Therefore, antibodies that bind α4 will bind α4β1 and antibodies that bind β1 will bind α4β1. Also, α4β1 goes by VLA-4 as well.

Butcher teach methods to control leukocyte extravasation by inhibiting leukocyte-endothelial interactions with adhesion molecule-specific antibodies (see entire document, particularly columns 1-8). Butcher teaches the in vivo inhibition leukocyte-entodthelial interactions and leukocyte extravasation by the MEL-14 monoclonal antibody (see column 2, particularly, lines 2-7 and 35-65). The MEL-14 antibody binds the α4 component of the claimed α4β1 specificity. Butcher teaches the methods of screening for inhibitory antibodies for adhesion-mediated events. Butcher differs from the claimed invention by not teaching α4β1-

specific or β1-specific antibodies per se.

In teaching the importance of α4β1 (VLA-4) in addition to α4 alone as involved in leukocyte adhesion during inflammation, Hemler et al. reviews the structure of VLA antigens including the association of distinct α subunits with a common β subunit (see entire document). Hemler et al. teaches that VLA proteins can interfere with cell attachment mechanism and inhibit cell binding to matrix or cell connective proteins and, in turn, inhibit tumor cell metastasis and interfere with immune cell function (page 5, paragraph 4). Hemler et al. teaches the importance of the VLA antigens, including VLA-4 in various inflammatory conditions (page 5, paragraph 4). Although, Hemler et al. disclose blocking by adhesion molecules proteins, Butcher teaches that adhesion molecule-specific antibodies also can block adhesion-mediated events.

In teaching the importance of the β1 specificity in leukocyte adhesion, Takada et al. exemplifies VLA β-specific antibodies can block cell adhesion to matrix proteins (see entire document, particulary page 607, column 2, paragraph 1).

It is noted that the cited references do not disclose the claimed P4C2 (α4-specific) and P4C10 (β1-specific) antibodies were not disclosed. The α4-specific antibodies taught by Butcher and Hemler et al. and the β1-specific antibodies taught by Takada et al. and Hemler et al. appear to be functionally equivalent to the instant claimed specificities. ~~It is the burden of the applicant to show the unobvious difference between the claimed invention and those that are generated or could be produced by the referenced methods~~.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting leukocyte-endothelial adhesion and leukocyte extravasation, as taught by Butcher with α4β1-specific (α4-specific or β1-specific) antibodies, as taught by the combined references, as therapeutic agents in treating inflammatory reactions, as taught by Butcher and Hemler et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. Claims 3 and 35 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher (U.S. Patent No. 5,403,919) in view of Hemler et al. (EP 0 330506) and Takada et al. (Nature, 1987) as applied to claims 1-5, 32 and 34-36 above and, in further view of Holzmann et al. (Immunol. Rev., 1989). Claims 1-5, 32, 34-36 are drawn to treating via methods of inhibiting leukocyte-endothelial adherence and leukocyte migration with $\alpha 4\beta 1$-specific antibodies.

Butcher, Hemler et al. and Takada et al. are taught supra in section 25. These references do not teach the P4C2 antibody per se.

In teaching the importance of $\alpha 4\beta 1$ (VLA-4) in human leukocyte adhesion, Holzmann et al. teach $\alpha 4$ is expressed by human VLA-4 (page 50, column 1 paragraph 2) and $\beta 1$ is common to the human fibronectin receptor and VLA proteins (page 52, paragraph 3). Further, $\alpha 4$-specific antibodies including the instant P4C2 antibody are able to inhibit human leukocyte-endothelial adhesion (page 55 including Figure 2).

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting leukocyte-endothelial adhesion and leukocyte extravasation, as taught by Butcher with $\alpha 4\beta 1$-specific ($\alpha 4$-specific or $\beta 1$-specific) antibodies, as taught by the combined references, including the P4C2 specificity, as taught by Holzmann et al., as therapeutic agents in treating inflammatory reactions, as taught by Butcher and Hemler et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

27. No claim allowed.

28. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
April 14, 1995

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
4/14/95